

# On a Distribution Function Arising in Computational Biology

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**ABSTRACT** Karlin and Altschul in their statistical analysis for multiple high-scoring segments in molecular sequences introduced a distribution function which gives the probability there are at least  $r$  distinct and consistently ordered segment pairs all with score at least  $x$ . For long sequences this distribution can be expressed in terms of the distribution of the length of the longest increasing subsequence in a random permutation. Within the past few years, this last quantity has been extensively studied in the mathematics literature. The purpose of this note is to summarize these new mathematical developments in a form suitable for use in computational biology.

*Dedicated to Barry McCoy on the occasion of his sixtieth birthday.*

## 1 The Distribution Function

Karlin and Altschul [8] in their statistical analysis for multiple high-scoring segments in molecular sequences, introduced the following distribution function: Let  $F(r; y)$  denote the probability that there are at least  $r$  distinct *and consistently ordered* segment pairs all with score at least  $x$ . They further introduced a parameter  $y = KNe^{-\lambda x}$  where  $K$  and  $\lambda$  are parameters related to the scoring system, see [8] for details. We use the parameter  $y$  without further reference to  $x$ . For long sequences ( $N \rightarrow \infty$ ) this distribution function is well approximated by [8]

$$F(r; y) = e^{-y} \sum_{k=r}^{\infty} \frac{y^k R_{k,r}}{k!^2}, \quad r = 1, 2, \dots, \quad (1.1)$$

where  $R_{k,r}$  is the number of permutations of the integers  $\{1, \dots, k\}$  that contain an increasing subsequence of length at least  $r$ . Let  $X_y$  denote a

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positive integer valued random variable such that

$$\text{Prob}(X_y \geq r) = F(r; y).$$

If  $R_{k,r}^c$  denotes the complement of  $R_{k,r}$ , i.e. the number of permutations  $\sigma \in S_k$  all of whose increasing subsequences have length strictly less than  $r$ , then clearly

$$\begin{aligned} R_{k,r}^c &= \# \{ \sigma \in S_k : \ell_k(\sigma) < r \} \\ &= \# \{ \sigma \in S_k : \ell_k(\sigma) \leq r-1 \} \\ &:= f_{k,r-1} \end{aligned}$$

where  $\ell_k(\sigma)$  is the length of the longest increasing subsequence in  $\sigma \in S_k$ .

**Remarks.**

1.  $F(r; y)$  is a distribution function in  $r$  with *parameter*  $y$ .
2. Dropping the requirement of consistent ordering has the effect of replacing  $R_{k,r}$  by  $k!$  in (1.1). Thus the segments are Poisson distributed with parameter  $y$ .

## 2 Summary of Known Properties

By convention,  $f_{0,r} := 1$  for all  $r$  and we note that  $f_{k,r} = k!$  if  $k \leq r$ . It is also convenient to introduce the parameter  $t \geq 0$ ,

$$y = t^2.$$

If we define

$$D_r(t) = \sum_{k=0}^{\infty} \frac{f_{k,r} t^{2k}}{k!^2}, \quad (2.1)$$

then

$$\begin{aligned} F(r; y) &= e^{-y} \sum_{k=r}^{\infty} \{k! - f_{k,r-1}\} \\ &= e^{-y} \sum_{k=r}^{\infty} \frac{y^k}{k!} - e^{-y} \sum_{k=r}^{\infty} \frac{f_{k,r-1} y^k}{k!^2} \\ &= e^{-y} \sum_{k=r}^{\infty} \frac{y^k}{k!} - e^{-y} \left( D_{r-1}(\sqrt{y}) - \sum_{k=0}^r \frac{y^k}{k!} \right) \\ &= 1 - e^{-y} D_{r-1}(\sqrt{y}). \end{aligned} \quad (2.2)$$

From Gessel [5] we know that  $D_r(t)$  is the  $r \times r$  Toeplitz determinant with symbol

$$f(z) = e^{t(z+1/z)}.$$

In the past few years,  $D_r$  has been extensively studied in connection with the limiting distribution of the length of the longest increasing subsequence of a random permutation, see Baik, Deift and Johansson [4] and Aldous and Diaconis [2, 3]. We now summarize some of these results. Gessel's theorem says that for all  $r = 1, 2, \dots$

$$D_r(t) = \det (b_{|i-j|})_{0 \leq i, j \leq r-1}$$

where  $b_j := I_j(2t)$  and  $I_j$  is the modified Bessel function. For *small*  $r$  one simply evaluates this determinant to obtain

$$\begin{aligned} F(1; y) &= 1 - e^{-y}, \\ F(2; y) &= 1 - b_0 e^{-y}, \\ F(3; y) &= 1 - (b_0^2 - b_1^2) e^{-y}, \\ F(4; y) &= 1 - (b_0^3 + 2b_1^2 b_2 - 2b_1^2 b_0 - b_0 b_2^2) e^{-y}. \end{aligned}$$

From (2.2) we see that

$$\phi_r(y) := e^{-y} D_r(\sqrt{y}) = \text{Prob}(X_y \leq r).$$

Johansson [7] has shown that for any given  $\varepsilon > 0$ , there exist  $C$  and  $\delta > 0$  such that

$$\begin{aligned} 0 \leq \phi_r(y) \leq C e^{-\delta y} & \quad \text{if} \quad (1 + \varepsilon)r < 2\sqrt{y}, \\ 0 \leq 1 - \phi_r(y) \leq \frac{C}{r} & \quad \text{if} \quad (1 - \varepsilon)r > 2\sqrt{y}. \end{aligned}$$

The breakthrough result of Baik-Deift-Johansson [4] is the sharper asymptotic result

$$\lim_{y \rightarrow \infty} \phi_{2\sqrt{y} + s y^{1/6}}(y) = F_2(s) \tag{2.3}$$

where  $F_2$  is the distribution function, first discovered by the present authors in the context of random matrix theory [10, 11] (see [13] for a review),

$$F_2(s) = \exp \left( - \int_s^\infty (x - s) q(x)^2 dx \right) \tag{2.4}$$

and  $q$  is the solution of the Painlevé II equation

$$q'' = sq + 2q^3 \tag{2.5}$$

satisfying  $q(s) \sim \text{Ai}(s)$  as  $s \rightarrow \infty$ . (Here  $\text{Ai}$  is the Airy function.) It is known that such a solution to (2.5) exists and is unique. A graph of the density  $dF_2/ds$  as well as some statistics of  $F_2$  can be found in [14]. In terms of the random variable  $X_y$  this says

$$\chi_y := \frac{X_y - 2\sqrt{y}}{y^{1/6}}$$

converges weakly to a random variable, call it  $\chi$ , with distribution function  $F_2$ . It was also proved that the scaled moments converge to the moments of  $F_2$  [4].

For finite  $r$  we now describe some results of Periwai and Shevitz [9], Hisakado [6], Tracy and Widom [12], and Adler and van Moerbeke [1]. (We follow the notation of [12].) We have the representation

$$\phi_r(y) = \exp \left( -4 \int_0^t \log(t/\tau) \tau (1 - \Phi_r(\tau)) d\tau \right), \quad y = t^2, \quad (2.6)$$

where  $\Phi_r$  as a function of  $t$  satisfies the equation

$$\Phi_r'' = \frac{1}{2} \left( \frac{1}{\Phi_r - 1} + \frac{1}{\Phi_r} \right) (\Phi_r')^2 - \frac{1}{t} \Phi_r' - 8\Phi_r(\Phi_r - 1) + 2 \frac{r^2}{t^2} \frac{\Phi_r - 1}{\Phi_r}. \quad (2.7)$$

We want the solution  $\Phi_r$  that satisfies

$$\Phi_r = 1 - \frac{t^{2r}}{(r!)^2} + O(t^{2r+1}), \quad t \rightarrow 0. \quad (2.8)$$

Setting

$$U_r^2 := 1 - \Phi_r,$$

we have the recursion relation, sometimes referred to as the discrete Painlevé II equation,

$$\frac{r}{t} U_r + (1 - U_r^2)(U_{r-1} + U_{r+1}) = 0, \quad r = 1, 2, \dots \quad (2.9)$$

The initial conditions for this recursion relation can be obtained from  $\phi_0 = e^{-y}$  and  $\phi_1 = b_0 e^{-y}$ . A computation shows<sup>†</sup>

$$U_0 = -1, \quad U_1 = \frac{I_1(2t)}{I_0(2t)}.$$

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<sup>†</sup>The signs of  $U_0$  and  $U_1$  are not fixed from  $\phi_0$  and  $\phi_1$ . In [12] the leading small  $t$  behavior of  $U_n$  is computed. We use this to fix the signs of  $U_0$  and  $U_1$ .

To make computational use of this distribution function, one needs *computationally* feasible formulas for the first few moments of  $X_y$  for all  $y$ ; and more generally, the distribution function itself. Here are some partial results. Of course,

$$\mathbf{E}(X_y) = \sum_{r=1}^{\infty} r (\phi_r - \phi_{r-1}). \quad (2.10)$$

From (2.6) and (2.8) it follows that

$$\phi_r(y) = 1 - \frac{y^{r+1}}{(r+1)!^2} + O(y^{r+2})$$

and thus

$$\mathbf{E}(X_y) = \sum_{r=1}^R r (\phi_r - \phi_{r-1}) + O(y^{R+1}).$$

Using the recursion relation (2.9) we can compute the first few  $U_n$ 's and expand these for small  $y$ . In this way we derive

$$\mathbf{E}(X_y) = y - \frac{1}{4}y^2 + \frac{1}{12}y^3 - \frac{7}{288}y^4 + O(y^5) \quad (2.11)$$

and similarly for the variance

$$\text{Var}(X_y) = y - \frac{3}{4}y^2 + \frac{17}{36}y^3 - \frac{67}{288}y^4 + O(y^5). \quad (2.12)$$

Note that the leading order terms are Poisson. Higher order expansion coefficients are given in Table 1.2.

From [4] we know that for large  $y$ , the essential contribution in (2.10) comes from  $r$  around  $2\sqrt{y}$ . Thus for  $y \rightarrow \infty$

$$\mathbf{E}(X_y) = 2\sqrt{y} + y^{1/6} \mathbf{E}(\chi) + o(y^{1/6}) \quad (2.13)$$

$$= 2\sqrt{y} - 1.77109 y^{1/6} + o(y^{1/6}) \quad (2.14)$$

where  $\chi$  has distribution function (2.4). We note for future reference,

$$\text{Var}(\chi) \approx 0.8132.$$

The small  $y$  expansion of  $\mathbf{E}(X_y)$  was computed through order 20. If we demand that the last coefficient in this expansion be less than, say,  $1/10$ , then  $y < 7.8$ . Evaluating this expansion at  $y = 7.8$  gives  $\mathbf{E}(X_y) = 3.66$  whereas the large  $y$  expansion evaluated at  $y = 7.8$  equals 3.09 which is a difference of 0.57. To improve the overlap of these two expansions, one needs to compute the error term in (2.13).

$x$	$y$	$\mathbf{E}(X_y)$	$\text{Var}(X_y)$
7.6	536.8	41.3	6.6
6.7	712.1	48.1	7.3
5.8	944.6	55.9	8.0

TABLE 1.1. For Karlin-Altschul parameters  $\lambda = 0.314$ ,  $K = 0.17$  and  $N = 34336$ , and three values of the normalized score  $x$ , the expected value and variance of  $X_y$  are computed using the large  $y$  expansions.

### 3 An Example

Karlin and Altschul give the parameters in their theory for the pairwise sequence comparison of the chicken gene X protein and the fowlpox virus antithrombin III homolog. The scoring system gives  $\lambda = 0.314$ ,  $K = 0.17$  and  $N = 34336$ . For the three alignments found (see Table 3 in [8]) the normalized scores (values of  $x$ ) are 7.6, 6.7 and 5.8. Using the above distribution function we compute the expected number of distinct consistently ordered segment pairs with at least normalized score  $x$ . The results are displayed in Table 1.1.

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$r$	$c_r^1$	$c_r^2$
1	1	1
2	$-\frac{1}{2^2}$	$-\frac{3}{2^2}$
3	$\frac{1}{2^2 3}$	$\frac{17}{2^2 3^2}$
4	$-\frac{7}{2^5 3^2}$	$-\frac{67}{2^5 3^2}$
5	$\frac{17}{2^6 3^2 5}$	$\frac{269}{2^6 3^2 5}$
6	$-\frac{619}{2^8 3^4 5^2}$	$-\frac{13 \cdot 19 \cdot 67}{2^8 3^4 5^2}$
7	$\frac{41}{2^7 3^2 5^2 7}$	$\frac{3491}{2^7 3^4 5^1 7}$
8	$-\frac{4001}{2^{12} 3^3 5^2 7^2}$	$-\frac{1064243}{2^{12} 3^4 5^2 7^2}$
9	$\frac{173 \cdot 313}{2^{14} 3^6 5^2 7^2}$	$\frac{28638487}{2^{14} 3^7 5^2 7^2}$
10	$-\frac{17 \cdot 62687}{2^{16} 3^8 5^3 7^2}$	$-\frac{41 \cdot 557 \cdot 17257}{2^{16} 3^8 5^3 7^2}$
11	$\frac{2823631}{2^{15} 3^8 5^4 7^2 11}$	$\frac{37 \cdot 61924123}{2^{15} 3^8 5^4 7^2 11}$
12	$-\frac{941 \cdot 407219}{2^{19} 3^{10} 5^4 7^2 11^2}$	$-\frac{17 \cdot 29 \cdot 286954607}{2^{19} 3^{10} 5^3 7^2 11^2}$
13	$\frac{6377893}{2^{17} 3^9 5^3 7^2 11^2 13}$	$\frac{206619709873}{2^{16} 3^{10} 5^4 7^2 11^2 13}$
14	$-\frac{11657 \cdot 1658989}{2^{22} 3^{10} 5^4 7^3 11^2 13^2}$	$-\frac{199735173503123}{2^{22} 3^{10} 5^4 7^3 11^2 13^2}$
15	$\frac{179 \cdot 257 \cdot 139493}{2^{20} 3^{11} 5^4 7^4 11^2 13^2}$	$\frac{479147 \cdot 50402324263}{2^{21} 3^{12} 5^6 7^4 11^2 13^2}$
16	$-\frac{37 \cdot 23593 \cdot 1363963}{2^{27} 3^{11} 5^6 7^4 11^2 13^2}$	$-\frac{59 \cdot 163363 \cdot 7608612619}{2^{27} 3^{11} 5^6 7^4 11^2 13^2}$
17	$\frac{43 \cdot 863 \cdot 701781161}{2^{30} 3^{12} 5^6 7^4 11^2 13^2 17}$	$\frac{27057479 \cdot 146285342603}{2^{30} 3^{12} 5^6 7^4 11^2 13^2 17}$
18	$-\frac{23 \cdot 5264671 \cdot 6578291}{2^{32} 3^{14} 5^6 7^4 11^2 13^2 17^2}$	$-\frac{307 \cdot 972530242052278499}{2^{32} 3^{14} 5^6 7^4 11^2 13^2 17^2}$
19	$\frac{1077161 \cdot 39636029}{2^{31} 3^{15} 5^4 7^4 11^2 13^2 17^2 19}$	$\frac{61 \cdot 83 \cdot 709 \cdot 7309 \cdot 37338914351}{2^{31} 3^{15} 5^6 7^4 11^2 13^2 17^2 19}$
20	$-\frac{229 \cdot 5189 \cdot 247913 \cdot 1229957}{2^{35} 3^{15} 5^8 7^4 11^2 13^2 17^2 19^2}$	$-\frac{239 \cdot 1181 \cdot 2161 \cdot 263188412702251}{2^{35} 3^{15} 5^7 7^4 11^2 13^2 17^2 19^2}$

TABLE 1.2. The number  $c_r^1$  is the coefficient of  $y^r$  in the small  $y$  expansion of  $\mathbf{E}(X_y)$  and  $c_r^2$  is the coefficient of  $y^r$  in the small  $y$  expansion of  $\text{Var}(X_y)$ .

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